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Original article

High residual platelet reactivity after switching from clopidogrel to low-dose prasugrel in Japanese patients with end-stage renal disease on hemodialysis

Yuji Ohno (MD)[a,*], Hideki Kitahara (MD, PhD)[a], Kenichi Fujii (MD, PhD)[a], Yukinori Kohno (MD, PhD)[b], Noritaka Ariyoshi (PhD)[c], Takeshi Nishi (MD, PhD)[a], Yoshihide Fujimoto (MD, PhD)[a], Yoshio Kobayashi (MD, PhD, FJCC)[a]

[a] Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan
[b] Department of Cardiovascular Medicine, Japan Community Health Care Organization Chiba Hospital, Chiba, Japan
[c] Department of Personalized Medicine and Preventive Healthcare Sciences, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

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ABSTRACT

Background: High on-treatment platelet reactivity (HPR) under clopidogrel treatment is frequently observed in hemodialysis (HD) patients. In such patients, 10 mg of prasugrel has reportedly inhibited platelet reactivity more adequately compared with 75 mg of clopidogrel. However, the efficacy of 3.75 mg prasugrel in Japanese HD patients is largely unknown.
Methods: A total of 41 Japanese coronary artery disease patients under HD who received aspirin and clopidogrel were enrolled. Clopidogrel was switched to 3.75 mg prasugrel. At day 14, prasugrel was switched to clopidogrel. Platelet reactivity was measured using VerifyNow assay (Accumetrics, San Diego, CA, USA) at baseline, day 14, and day 28. VerifyNow P2Y12 reaction units (PRU) >208 was defined as HPR.
Results: The PRU level on prasugrel therapy was significantly lower than that on clopidogrel therapy before switching (219.1 ± 62.3 PRU vs. 238.2 ± 68.0 PRU, $p = 0.02$). Although the prevalence of HPR was numerically lower on prasugrel therapy compared with clopidogrel therapy before and after switching, the differences did not reach a statistical significance (57.6% vs. 75.7% vs. 74.2%, $p = 0.13$). Even under prasugrel treatment, more than half of patients showed HPR.
Conclusions: Although low-dose prasugrel had somewhat better antiplatelet effect than clopidogrel, it could not significantly improve the prevalence of HPR in Japanese HD patients. Higher doses of prasugrel might be needed to achieve adequate platelet inhibition in this high thrombotic risk population.

Introduction

High on-treatment platelet reactivity (HPR) on antiplatelet therapy has been associated with adverse cardiovascular events including stent thrombosis in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) [1–9]. HPR under clopidogrel treatment is well recognized [10–13], and this inadequate platelet inhibition is relatively frequent in Japanese patients due to the genetic polymorphism of CYP2C19 [14]. Prasugrel is a newer-generation thienopyridine that has more potent antiplatelet effect with less interpatient variability compared with clopidogrel [15]. Considering increased bleeding risk with other thrombotic agents in Japanese patients [16], the dose of prasugrel in Japan was determined as approximately one-third of that used in Western patients. In our previous study, stronger platelet inhibition by low-dose prasugrel compared with standard-dose clopidogrel was confirmed by switching these two agents in Japanese patients with stable CAD [17].

Patients with chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD) on hemodialysis (HD), are at

* Corresponding author at: Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan.
E-mail address: yuji.o.chiba@gmail.com (Y. Ohno).

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high risk of cardiovascular events including stent thrombosis [18–20]. HPR under clopidogrel treatment is more frequently observed in patients with ESRD on HD than in any other populations [21–23]. In such patients, 10 mg prasugrel reportedly inhibits platelet reactivity more adequately than 75 mg clopidogrel [24]. Although we also previously reported 3.75 mg prasugrel achieved a consistently lower platelet reactivity despite the presence of mild to moderate CKD [25], the antiplatelet effect of low-dose prasugrel in Japanese HD patients is unclear. Thus, the aim of this study was to evaluate the pharmacodynamic effects of changing from 75 mg clopidogrel to 3.75 mg prasugrel in Japanese patients with ESRD on HD.

Methods

Study design and patients

This is a prospective, multi-center, open-label study to evaluate antiplatelet effects when clopidogrel is switched to prasugrel in stable CAD patients on chronic HD undergoing PCI. Patients were eligible for the study if they were on regular maintenance HD 3 times a week for ≥6 months and between 20 and 80 years of age, and had been taking daily aspirin and clopidogrel for ≥14 days after PCI. Patients were excluded in the presence of any of the following: contraindications to prasugrel, severe liver dysfunction, body weight ≤50 kg, platelet count ≤100,000/μL, acute coronary syndrome event within 4 weeks, PCI or coronary artery bypass graft surgery within 4 weeks or scheduled during the study period, chronic oral anti-coagulation treatment, scheduled thrombolysis treatment, changed condition of HD within 2 weeks or planned to change during the study period, taking ticlopidine or cilostazol, and lactating or pregnancy.

A flow chart of this study is shown in Fig. 1. Patients who received aspirin (100 mg daily) and clopidogrel (75 mg daily) for ≥14 days underwent platelet reactivity measurement. Clopidogrel was switched to 3.75 mg prasugrel (maintenance dose in Japanese patients). Platelet reactivity measurement and safety evaluation were done on day 14. Direct switching from prasugrel to 75 mg clopidogrel was then performed without an intervening washout period. At day 28, patients received clinical and laboratory assessment as performed on the day 14 visit. Aspirin remained unchanged throughout the study period.

The protocol was approved by the institutional review boards at Chiba University Hospital and the other institutions conducting this study. The study was conducted in accordance with regulatory standards and ethics guidelines for clinical studies according to the Declaration of Helsinki. All patients provided written informed consent. The independent data center of Chiba University Hospital collected and managed data. The present study was registered at the University Hospital Medical Information Network Clinical Trials Registry (number: UMIN 000022139) in Japan.

Platelet function and genotyping assay

Peripheral venous blood samples were drawn through a short venous catheter inserted into forearm immediately before HD. Platelet function was assessed using the VerifyNow assay (Accumetrics, San Diego, CA, USA). This measures adenosine diphosphate-induced platelet function, reported as P2Y12 reaction units (PRU). Based on previous studies in which thresholds for platelet reactivity were identified, VerifyNow P2Y12>208 PRU was defined as HPR.

Genotyping of CYP2C19*2 (rs4244285, c681G>A) and CYP2C19*3 (rs4986893, c636G>A) was performed using the newly developed genotyping system, GTS-7000 (Shimadzu, Kyoto, Japan), with 1 μL of the rest of whole blood used for laboratory testing. This system detects single-nucleotide polymorphisms on direct polymerase chain reaction amplification with no requirement for DNA extraction. The patients were classified into 3 genotype groups: extensive metabolizer (EM) (*1/*1), intermediate metabolizer (IM) (*1/*2 or *1/*3), and poor metabolizer (PM) (*2/*2, *2/*3, or *3/*3). The use of blood samples for genotyping was approved (approval No. 631) by the Biomedical Research Ethics Committee of the Graduate School of Medicine, Chiba University, in accordance with the Ethics Guidelines for Human Genome and Gene Analyses Research in Japan.

Study endpoints

The primary efficacy endpoint was a comparison of the prevalence of HPR between clopidogrel treatment at study entry and prasugrel maintenance treatment. Secondary endpoints included the prevalence of HPR and PRU level among clopidogrel treatment at study entry, prasugrel maintenance treatment, and clopidogrel treatment at last follow-up. The prevalence of HPR with clopidogrel and prasugrel treatment was also compared among the 3 CYP2C19 polymorphism groups. The safety endpoints were the frequency of bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria, definite or probable stent thrombosis according to the Academic Research Consortium definition, and myocardial infarction according to the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) criteria during the study period.

Statistical analysis

Based on previous studies, we estimated the rate of HPR as 60% on clopidogrel therapy and 28.5% on prasugrel therapy in dialysis patients, respectively. On the basis of these assumptions, we estimated that 41 patients were required for a power of 80% and a 2-sides alpha level of 0.05, assuming a dropout rate of 10%.

Continuous variables are presented as a mean ± standard deviation (SD) and were compared using paired or Student's *t*-test. Categorical variables are presented as *n* (%) and were compared using McNurmer test, or Wilcoxon rank sum test. All data were analyzed using STATA 14.2 software (StataCorp LP, College Station, TX, USA).

Results

Between July 2016 and January 2017, 41 HD patients were enrolled in 8 institutions. Flow of patients in this study is shown in Fig. 1. After enrolment, 2 patients were excluded because of screening error, and 2 were discontinued from the study before taking prasugrel because of withdrawal and urgent hospitalization for heart failure. During the study period, antiplatelet therapy along the protocol was discontinued in 5 patients. Two of these patients discontinued to take prasugrel because of adverse events, which were fundus bleeding and eruption. The fundus bleeding was found during taking prasugrel, although it is uncertain when the bleeding occurred. This bleeding was classified into minimal according to the TIMI bleeding criteria. The reasons for other discontinued subjects were patient's wish, scheduled hospitalization, and discontinuation of prasugrel for minor surgery. There were no adverse cardiovascular events during the study, except that 1 heart failure hospitalization that occurred before taking prasugrel. Patient characteristics of this study are shown in Table 1.

The prevalence of HPR was numerically lower on prasugrel maintenance therapy compared with clopidogrel therapy before and after switching, although the differences did not reach a statistical significance (Fig. 2). The PRU level on prasugrel therapy was significantly lower than that on clopidogrel therapy before

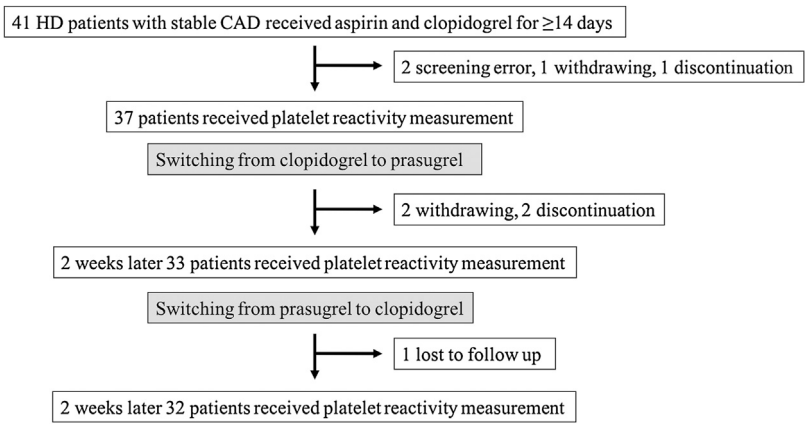

Fig. 1. Flow chart of this study. HD, hemodialysis; CAD, coronary artery disease.

switching, and tended to be lower than that on clopidogrel therapy after switching (Fig. 3). In this study, 1 patient had a high fever due to a common cold during prasugrel treatment. Because such inflammatory changes increase platelet reactivity [26], a post-hoc analysis excluding this patient was performed. In this analysis, prasugrel significantly decreased the prevalence of HPR compared with clopidogrel before switching (56.3% vs. 77.1%, $p = 0.03$). The PRU level on prasugrel therapy was also significantly lower than that on clopidogrel therapy before switching (241.3 ± 66.7 vs. 219.1 ± 63.3, $p < 0.01$).

Fig. 4 shows the patient number and percentage of HPR and non-HPR at 3 points. Of 28 patients with HPR on clopidogrel therapy, 18 patients (75%) had HPR even under prasugrel treatment.

Table 2 shows the results of genotyping of *CYP2C19*. The genotype of *CYP2C19* polymorphism had a significant impact on the rate of HPR under clopidogrel treatment. On the other hand, the relationship between the rate of HPR under prasugrel treatment and the genotype groups of *CYP2C19* polymorphism was not significant (Fig. 5). The PRU level on prasugrel therapy was significantly lower than that on clopidogrel therapy before switching in PM patients (268.3 ± 27.7 vs. 224.5 ± 45.9, $p = 0.03$), however in EM and IM patients, prasugrel therapy did not reduce platelet reactivity significantly (214.5 ± 84.1 vs. 204.7 ± 74.9, $p = 0.54$, 243.3 ± 64.0 vs. 226.9 ± 60.1, $p = 0.10$).

Table 1
Patient characteristics.

Age (years)	65.2 ± 9.1
Male	37 (90)
Height (cm)	165.8 ± 6.0
BMI	25.7 ± 4.7
Comorbidities	
Hypertension	30 (81)
Diabetes mellitus	30 (81)
Dyslipidemia	24 (65)
Peripheral artery disease	13 (35)
Cause of end-stage renal disease	
Diabetic mellitus	30 (81)
Duration of hemodialysis (years)	6.73 ± 5.5
Prior myocardial infarction	17 (46)
Prior ischemic stroke	4 (11)
Prior PCI	37 (100)
Prior CABG	2 (5)
Medication	
ACEi/ARB	17 (46)
Beta blockers	17 (46)
Calcium channel blockers	17 (46)
Statin	18 (49)
Proton pump inhibitors	28 (76)
Other antiplatelet agents	5 (14)

Data given as mean ± SD or *n* (%).
BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Other antiplatelet agents include limaprost, sarpogrelate, beraprost, and eicosapentanoic acid.

Discussion

There were 3 major findings in the present study: (i) clopidogrel treatment achieved adequate platelet inhibition only in one fourth of HD patients; (ii) although switching from clopidogrel to 3.75 mg prasugrel lowered the PRU level, the prevalence of HPR was not significantly reduced, resulting in that more than half of patients remained HPR even on prasugrel treatment; and (iii) while CYP2C19 polymorphism had a significant impact on platelet reactivity with clopidogrel in HD patients, as reported in the general population, this polymorphism did not affect the efficacy of prasugrel.

The presence of HPR on antiplatelet therapy is associated with worse cardiovascular outcomes after PCI not only in general population [8], but also in CKD patients [27,28]. In particular, HD patients have a high prevalence of HPR, which might be one of the reasons why HD is an independent predictor for adverse events, including stent thrombosis [19]. Previous reports showed that 60%-80% of ESRD or HD patients had HPR under clopidogrel treatment [21,22]. This prevalence of HPR is consistent with our results in HD patients under clopidogrel treatment. The inadequate response to clopidogrel in HD patients could be accounted for by several reasons, such as dysfunction of adenosine diphosphate receptors [29] and exposure of blood to the dialysis circuit itself [30].

The loading and maintenance doses of prasugrel for Japanese patients (20 and 3.75 mg, respectively) are approximately one-third of those for Western patients. In the PRASugrel compared with clopidogrel For Japanese patIenTs with Acute Coronary Syndrome undergoing PCI (PRASFIT-ACS) study and the PRASugrel compared with clopidogrel For Japanese patIenTs with CAD undergoing Elective PCI (PRASFIT-Elective) study, the clinical efficacy and safety of low-dose prasugrel in Japanese patients were reported [31,32]. In our previous report, 3.75 mg prasugrel achieved stronger platelet inhibition than clopidogrel in Japanese patients with preserved renal function [17]. Furthermore, its subanalysis demonstrated the consistently lower platelet reactivity by low-dose prasugrel compared with clopidogrel despite the presence of mild to moderate CKD [25]. However, these previous studies with low-dose prasugrel in Japan excluded ESRD patients

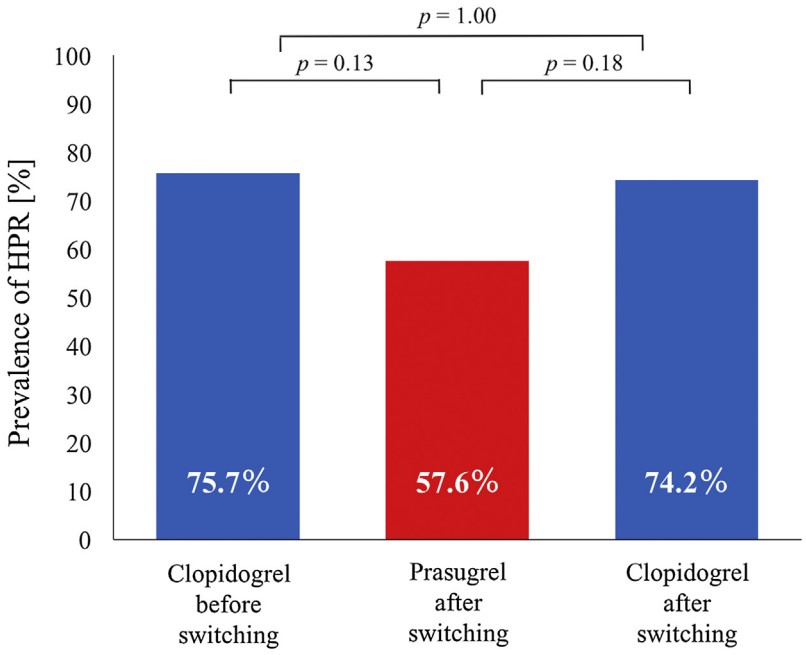

Fig. 2. Prevalence of high on-treatment platelet reactivity (HPR) between clopidogrel treatment before switching, prasugrel maintenance treatment, and clopidogrel treatment at the last follow-up.

on HD. In the present study, although low-dose prasugrel showed modestly superior antiplatelet effect than standard-dose clopidogrel, more than half of the patients showed HPR even under prasugrel treatment, even in the post-hoc analysis excluding 1 patient with a high fever. In a previous Western study, only 19% of HD patients demonstrated hypo-responsiveness under 10 mg prasugrel in ESRD patients on HD, even though that study enrolled only patients with HPR under clopidogrel treatment [24]. In contrast to the rate of HPR under clopidogrel in the present study, which is consistent with the results of Western studies, the rate of HPR under 3.75 mg prasugrel in Japanese patients seems to be much higher than with 10 mg prasugrel in Western patients [24]. Previously, Neubauer et al. showed that doubling of the 10 mg prasugrel was effective with adequate platelet inhibition without bleeding events in all 4 patients with prasugrel resistance [33]. Since the antiplatelet effect of prasugrel is dose-dependent [34], higher doses might be needed in order to obtain adequate platelet inhibition in Japanese HD patients.

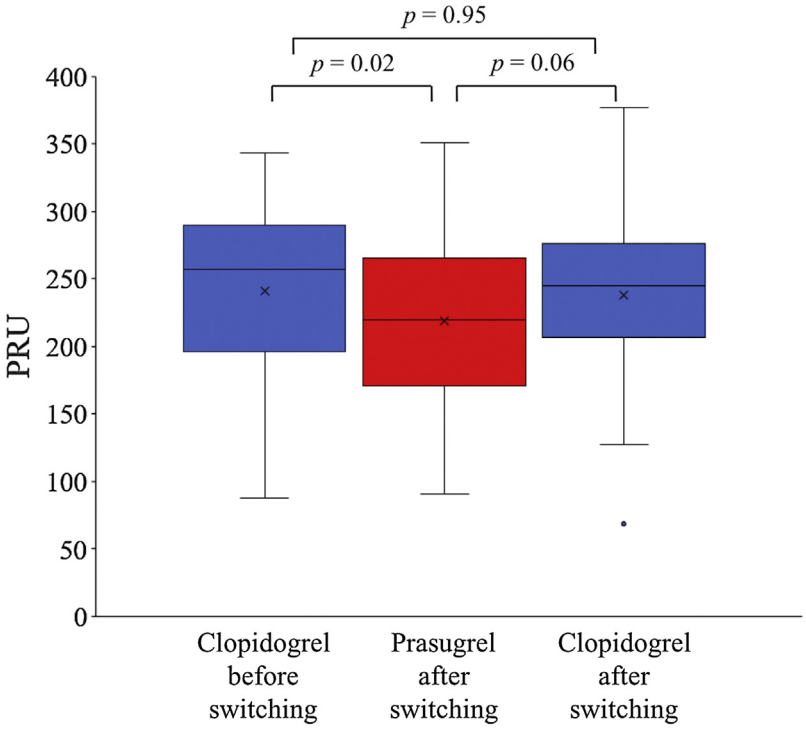

Fig. 3. P2Y12 reaction units (PRU) between clopidogrel treatment before switching, prasugrel maintenance treatment, and clopidogrel treatment at the last follow-up.

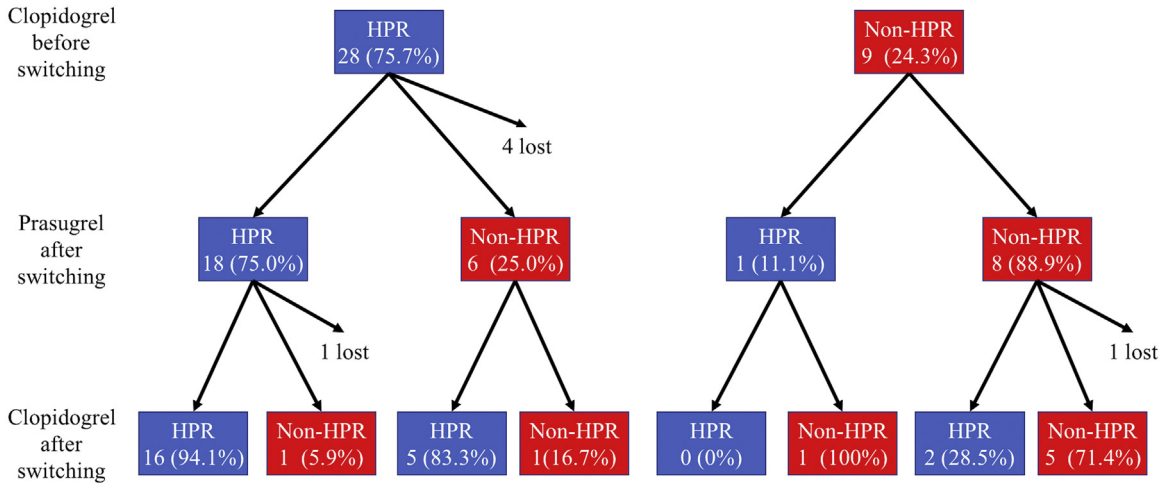

Fig. 4. Patient distribution with regard to high on-treatment platelet reactivity (HPR) and non-HPR on clopidogrel treatment at before switching, prasugrel maintenance treatment, and clopidogrel treatment at the last follow-up.

Both clopidogrel and prasugrel are prodrugs of $P2Y_{12}$ receptor inhibitor. The majority of clopidogrel is shunted by esterases to a dead-end inactive pathway, with a remaining prodrug requiring a 2-step conversion to its active metabolite, which is regulated by the cytochrome P450 (CYP) system. On the other hand, prasugrel is an inactive prodrug that is transformed first through hydrolization by esterases, followed by a single CYP-dependent oxidative step into its active metabolite [35]. Although CYP2C19 genotype has been associated with insufficient platelet inhibition to clopidogrel treatment [36], this genetic variation has not shown a significant influence on the response to prasugrel [37]. No significant effect of CYP2C19 polymorphism on the efficacy of 3.75 mg prasugrel was observed in our HD population, and this phenomenon is consistent with the reports of the preserved renal function population on 3.75 mg prasugrel [17] and HD patients on 10 mg prasugrel [24]. The insufficient antiplatelet effect of prasugrel in HD patients observed in the present study seems to be derived from other mechanisms rather than CYP2C19 polymorphism. In the analysis based on CYP2C19 polymorphism, prasugrel significantly reduced the PRU level compared with clopidogrel only in PM patients, not in EM and IM patients. Although this analysis includes a small number of patients, this finding suggests that superior antiplatelet effect of prasugrel is shown especially in PM patients.

Proton pump inhibitors (PPIs) were administered in 78% of participants in our study. It is possible that this high percentage of PPI administration could affect the PRU level under clopidogrel treatment. There is concern that PPIs may attenuate the antiplatelet effect of clopidogrel via CYP2C19, since this drug is also metabolized by CYP2C19 as with clopidogrel. In fact, the sub-analysis of ADAPT-DES registry showed that the concomitant administration of PPI was associated with high PRU level [38]. Conversely, the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) [39], which was a randomized, double-blind, double-dummy, placebo-controlled trial, showed no significant increase in the risk of cardiovascular events with concomitant use of clopidogrel and omeprazole. Although pharmacodynamics and observational studies support an interaction between PPI and clopidogrel, results from randomized clinical trials are conflicting. However, importantly, no interaction between concomitant use of prasugrel and PPI has been reported. The high percentage of PPI administration might partially contribute to the higher PRU level under clopidogrel treatment compared with prasugrel treatment in our study.

Safety of antiplatelet therapy is also a major concern in HD patients, because not only thrombotic risk but also bleeding risk is increased in this population. In our study, any major bleeding was not observed, and only one patient had minor bleeding during the study period, although our study did not have enough size and duration to assess the safety. Whereas it may be effective to increase prasugrel dose in the HD population at high cardiovascular risk, there should be a trade-off between decrease in thrombotic events and increase in bleeding events. Further studies are needed to evaluate the safety as well as efficacy of higher dose of prasugrel in Japanese HD patients.

Table 2
Results of genotyping.

		n (%)	*n* (%)
*1/*1	EM	11 (30)	11 (30)
*1/*2	IM	19 (51)	14 (38)
*1/*3			5 (14)
*2/*2	PM	7 (19)	2 (5)
*2/*3			4 (11)
*3/*3			1 (3)

Data given as *n* (%).
EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Study limitations

There are several limitations in the present study. First, this study was small and not cross-over designed. Second, this was a pharmacodynamic study, and did not have enough size to assess the efficacy or safety. Third, we defined HPR as PRU>208 based on previous Western studies. In Japanese, post-hoc analysis of the PRASFIT-ACS showed that PRU>262 was identified as the optimal cut-off value to predict major cardiovascular events after PCI [40]. However, the optimal cut-off value of in this HD population has not been established. There was only a small study demonstrating that PRU>235 predicted major adverse cardiovascular events in the HD population [41]. Even using this cut-off value, the main results of our study were not changed.

Conclusions

While low-dose prasugrel had somewhat better antiplatelet effect than standard-dose clopidogrel, it could not achieve adequate platelet inhibition, with higher prevalence of HPR than that previously reported with standard-dose prasugrel in Western HD patients, in Japanese HD patients with stable CAD.

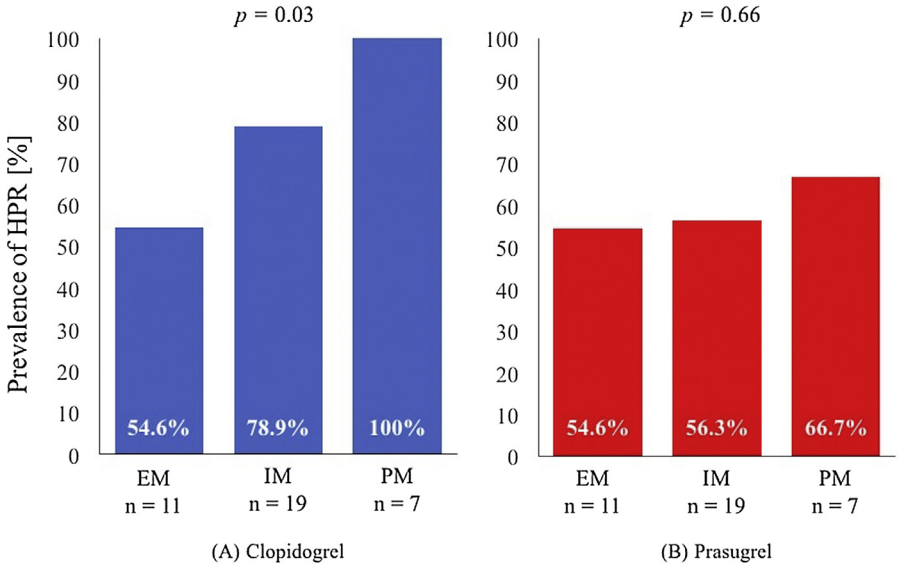

Fig. 5. Impact of CYP2C19 polymorphism genotype on high on-treatment platelet reactivity (HPR) with (A) clopidogrel and (B) prasugrel. EM, extensive metabolizer genotype; IM, intermediate metabolizer genotype; PM, poor metabolizer genotype.

Conflict of interest

Yoshio Kobayashi received research funding from Daiichi-Sankyo (Tokyo, Japan) and Sanofi (Paris, France).

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References

[1] Gurbel PA, Bliden KP, Guyer K, Cho PW, Zaman KA, Kreutz RP, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the PREPARE POST-STENTING Study. J Am Coll Cardiol 2005;46:1820–6.
[2] Hochholzer W, Trenk D, Bestehorn H-P, Fischer B, Valina CM, Ferenc M, et al. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. J Am Coll Cardiol 2006;48:1742–50.
[3] Cuisset T, Frere C, Quilici J, Barbou F, Morange PE, Hovasse T, et al. High post-treatment platelet reactivity identified low-responders to dual antiplatelet therapy at increased risk of recurrent cardiovascular events after stenting for acute coronary syndrome. J Thromb Haemost 2006;4:542–9.
[4] Price MJ, Endemann S, Gollapudi RR, Valencia R, Stinis CT, Levisay JP, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008;29:992–1000.
[5] Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 2008;52:1128–33.
[6] Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 2009;119:237–42.
[7] Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJT, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754–62.
[8] Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614–23.
[9] Tantry US, Bonello L, Aradi D, Price MJ, Jeong Y-H, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–73.
[10] Müller I, Besta F, Schulz C, Massberg S, Schönig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783–7.
[11] Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
[12] Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Bhatt DL, Topol EJ. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005;45:246–51.
[13] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
[14] Jinnai T, Horiuchi H, Makiyama T, Tazaki J, Tada T, Akao M, et al. Impact of CYP2C19 polymorphisms on the antiplatelet effect of clopidogrel in an actual clinical setting in Japan. Circ J 2009;73:1498–503.
[15] Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann F-J, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923–32.
[16] Suzuki S, Yamashita T, Kato T, Fujino T, Sagara K, Sawada H, et al. Incidence of major bleeding complication of warfarin therapy in Japanese patients with atrial fibrillation. Circ J 2007;71:761–5.
[17] Nishi T, Ariyoshi N, Nakayama T, Fujimoto Y, Sugimoto K, Takahara M, et al. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in Japanese patients with stable coronary artery disease. Circ J 2015;79:2439–44.
[18] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[19] Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T, et al. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation 2010;122:52–61.
[20] Lee JM, Kang J, Lee E, Hwang D, Rhee T-M, Park J, et al. Chronic kidney disease in the second-generation drug-eluting stent era: pooled analysis of the Korean Multicenter Drug-Eluting Stent Registry. JACC: Cardiovasc Interv 2016;9:2097–109.
[21] Muller C, Caillard S, Jesel L, Ghannudi El S, Ohlmann P, Sauleau E, et al. Association of estimated GFR with platelet inhibition in patients treated with clopidogrel. Am J Kidney Dis 2012;59:777–85.
[22] Alexopoulos D, Xanthopoulou I, Panagiotou A, Komninakis D, Germanos N, Goudas P, et al. Prevalence of inadequate platelet inhibition by clopidogrel in patients receiving hemodialysis. Am J Kidney Dis 2012;59:469–71.
[23] Guo LZ, Kim MH, Shim CH, Choi SY, Serebruany VL. Impact of renal impairment on platelet reactivity and clinical outcomes during chronic dual antiplatelet therapy following coronary stenting. Eur Heart J Cardiovasc Pharmacother 2016;2:145–51.
[24] Alexopoulos D, Panagiotou A, Xanthopoulou I, Komninakis D, Kassimis G, Davlouros P, et al. Antiplatelet effects of prasugrel vs. double clopidogrel in patients on hemodialysis and with high on-treatment platelet reactivity. J Thromb Haemost 2011;9:2379–85.

[25] Nishi T, Ariyoshi N, Nakayama T, Fujimoto Y, Sugimoto K, Wakabayashi S, et al. Impact of chronic kidney disease on platelet inhibition of clopidogrel and prasugrel in Japanese patients. J Cardiol 2017;69:752–5.
[26] Kreutz RP, Tantry US, Bliden KP, Gurbel PA. Inflammatory changes during the "common cold" are associated with platelet activation and increased reactivity of platelets to agonists. Blood Coagul Fibrinolysis 2007;18:713–8.
[27] Morel O, Ghannudi El S, Jesel L, Radulescu B, Meyer N, Wiesel ML, et al. Cardiovascular mortality in chronic kidney disease patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12 inhibition by clopidogrel. J Am Coll Cardiol 2011;57:399–408.
[28] Htun P, Fateh-Moghadam S, Bischofs C, Banya W, Müller K, Bigalke B, et al. Low responsiveness to clopidogrel increases risk among CKD patients undergoing coronary intervention. J Am Soc Nephrol 2011;22:627–33.
[29] Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabaté M, Ferreiro JL, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J Am Coll Cardiol 2010;55:1139–46.
[30] Aggarwal A, Kabbani SS, Rimmer JM, Gennari FJ, Taatjes DJ, Sobel BE, et al. Biphasic effects of hemodialysis on platelet reactivity in patients with end-stage renal disease: a potential contributor to cardiovascular risk. Am J Kidney Dis 2002;40:315–22.
[31] Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome. Circ J 2014;78:1684–92.
[32] Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, et al. Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. Circ J 2014;78:2926–34.
[33] Neubauer H, Kaiser A, Busse B, Mügge A. Identification, evaluation and treatment of prasugrel low-response after coronary stent implantation—a preliminary study. Thromb Res 2010;126:e389–91.
[34] Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J 2005;27:1166–73.
[35] Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. J Clin Pharmacol 2010;50:126–42.
[36] Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849–57.
[37] Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744–52.
[38] Weisz G, Smilowitz NR, Kirtane AJ, Rinaldi MJ, Parvataneni R, Xu K, et al. Proton pump inhibitors, platelet reactivity, and cardiovascular outcomes after drug-eluting stents in clopidogrel-treated patients: the ADAPT-DES study. Circ Cardiovasc Interv 2015;8. pii: e001952.
[39] Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909–17.
[40] Nakamura M, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Optimal cutoff value of P2Y12 reaction units to prevent major adverse cardiovascular events in the acute periprocedural period: post-hoc analysis of the randomized PRASFIT-ACS study. Int J Cardiol 2015;182:541–8.
[41] Konishi A, Shinke T, Otake H, Takaya T, Osue T, Kinutani H, et al. Impact of residual platelet reactivity under clopidogrel treatment for lesions and the clinical outcome after drug-eluting stent implantation in patients with hemodialysis. J Cardiol 2016;67:531–7.